General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium guidelines for *HLA-B* genotype and carbamazepine dosing.

Bibliographic Source(s)

Leckband SG, Kelsoe JR, Dunnenberger HM, George AL Jr, Tran E, Berger R, Muller DJ, Whirl-Carrillo M, Caudle KE, Pirmohamed M. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing. Clin Pharmacol Ther. 2013 Sep;94(3):324-8. [39 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Genetic Test Interpretation

Clinical genotyping tests exist for identifying *human leukocyte antigen B (HLA-B)* alleles, including *HLA-B*15:02*. The *HLA-B*15:02* allele predisposes to the development of carbamazepine-induced Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) but is not known to affect either carbamazepine pharmacokinetics or the development of other types of cutaneous adverse reactions (see the original guideline document for additional details). Genotyping results are presented as "positive" if one or two copies of *HLA-B*15:02* are present or as "negative" if no copies of *HLA-B*15:02* are present. There is no intermediate genotype or phenotype. Phenotype assignments for *HLA-B*15:02* genotypes are summarized in Table 1, below.

Table 1. Assignment of Likely *HLA-B* Phenotypes Based on Genotypes

Genotype	Likely Phenotype	Examples of Diplotypes
Noncarrier of *HLA-B*15:02*. No **15:02* alleles reported, often reported as "negative" on a genotyping test.	Homozygous for an allele other than **15:02*; at "normal" or reduced risk of carbamazepine-induced SJS/TEN	*X/*X[a]
Carrier of *HLA-B*15:02*. One or two **15:02* alleles, often reported as "positive" on a genotyping test.	Heterozygote or homozygous variant; at significantly increased risk of carbamazepine-induced SJS/TEN	*15:02/*X[a], *15:02/*15:02

HLA-B, *human leukocyte antigen B*; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

See Supplementary Material online for estimates of genotype frequencies among different ethnic/geographic groups (see the "Availability of Companion Documents" field).

[a]Where *X = any genotype other than **15:02*.

Therapeutic Recommendations

Currently, the Food and Drug Administration (FDA) recommends that "patients with ancestry in at-risk populations should be screened for the presence of *HLA-B*15:02* allele prior to starting carbamazepine" (see the FDA Web site). Individuals at highest risk are those of Han Chinese descent, followed by those in Vietnam, Cambodia, the Reunion Islands, Thailand, India (specifically Hindus), Malaysia, and Hong Kong. The frequency of *HLA-B*15:02* is very low in other populations (see Supplementary Table S2 online for frequency information [see the "Availability of Companion Documents" field]). However, it is important that the prescribing physician bear in mind that many people may be unaware of or fail to disclose more distant Asian ancestry in their families. In addition, much of the evidence (summarized in Supplementary Table S3 online [see the "Availability of Companion Documents" field]) linking *HLA-B*15:02* to SJS/TEN was generated in both children and adults. Therefore, regardless of ancestry or age of the individual, if the genetic testing results are "positive" for the presence of at least one copy of the *HLA-B*15:02* allele, it is recommended that a different agent be used depending on the underlying disease, unless the benefits clearly outweigh the risk (see Table 2, below).

Carbamazepine-induced SJS/TEN usually develops within the first three months of therapy; therefore, patients who have been taking carbamazepine for longer than 3 months without developing cutaneous reactions are at low risk (but not zero) of carbamazepine-induced adverse events in the future, regardless of *HLA-B*15:02* status.

Table 2. Carbamazepine Therapy Recommendations Based on *HLA-B* Genotype

Genotype	Phenotypic Implications	Therapeutic Recommendations	Classification of Recommendations
Noncarrier of *HLA-B*15:02*	Normal or reduced risk of carbamazepine-induced SJS/TEN	Use carbamazepine per standard dosing guidelines	**Strong**
Carrier of *HLA-B*15:02*	Increased risk of carbamazepine-induced SJS/TEN	If patient is carbamazepine-naive, do not use carbamazepine[a]	**Strong**
		If patient has previously used carbamazepine for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine	**Optional**

HLA-B, *human leukocyte antigen B*; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis

[a]Alternative medications such as phenytoin, fosphenytoin, oxcarbazepine, eslicarbazepine acetate, and lamotrigine have some evidence linking SJS/TEN with the *HLA-B*15:02* allele, and thus caution should be used in choosing alternatives to carbamazepine (see Supplementary Material online for details [see the "Availability of Companion Documents" field]).

Recommendations for Incidental Findings

Several drugs structurally and therapeutically similar to carbamazepine have also been associated with SJS/TEN and *HLA-B*15:02*. The drug-specific evidence linking *HLA-B*15:02* and SJS/TEN is discussed in the Supplementary Material online (see the "Availability of Companion Documents" field) and may have implications for choosing alternatives to carbamazepine in those who carry the *HLA-B*15:02* allele.

In one study, the *HLA-B*07:02* allele was absent in patients with carbamazepine-induced SJS/TEN but was present at frequencies of 18% in the control group and 14% in those with a mild hypersensitivity reaction, leading the authors to conclude that *HLA-B*07:02* may protect against carbamazepine-induced SJS/TEN. However, there is no course of action suggested based on this genotype.

Definitions:

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the

recommended course of action.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Epilepsy and other seizure disorders, trigeminal neuralgia, and bipolar disorder

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Allergy and Immunology

Dermatology

Family Practice

Internal Medicine

Medical Genetics

Pharmacology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide information to allow the interpretation of clinical *human leukocyte antigen B (HLA-B)*15:02* genotype tests so that the results can be used to guide the use of carbamazepine

Target Population

Patients with epilepsy and other seizure disorders, trigeminal neuralgia, or bipolar disorder who are being considered for carbamazepine therapy

Interventions and Practices Considered

Carbamazepine dosing based on *human leukocyte antigen B (HLA-B)*15:02* genotype

Major Outcomes Considered

- Risk of Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in relation to *human leukocyte antigen B (HLA-B)* genotype
- Adverse effects of carbamazepine in relation to *HLA-B* genotype

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Patient Registry Data

Description of Methods Used to Collect/Select the Evidence

A search was conducted on the PubMed database (1966 to December 2012) and the Ovid MEDLINE (1950 to December 2012) database for keywords ([HLA or HLA-B or *HLA-B*15:02*] AND [carbamazepine]). A more general search was also conducted using the search terms ([carbamazepine hypersensitivity] OR [carbamazepine Stevens-Johnson]).

A table of frequencies of the *human leukocyte antigen B (HLA-B)*15:02* allele in different ethnic populations around the world was assembled from several sources. Frequencies were included from the Allele Frequencies in Worldwide Populations Web site that lists frequency data for *HLA-B*15:02* from 100 different samples and populations. Where possible, the original paper from which the allele frequencies were obtained was reviewed for the inclusion criteria listed below. Allele frequencies were also obtained by conducting a search of the PubMed database (1966 to June 2012) and Ovid MEDLINE (1950 to June 2012) using the following criteria: ([HLA or HLA-B or *HLA-B*15:02*] AND [genotype or allele or frequency]) with filter limits set to retrieve "full-text" and "English" literature. Studies from both sources were considered for inclusion if, 1) the ethnicity of the population was clearly indicated; 2) either allele frequencies or alleles for *HLA-B* genotypes were reported; 3) the method by which *HLA-B* was genotyped was reliable and proven; 4) the sample population consisted of at least 50 individuals; 5) the study represented publication of novel data, not literature reviews or meta-analyses of previously published data; and 6) the population studied did not have a concomitant disease (such as an autoimmune condition) that would be expected to result in a distribution of *HLA-B* alleles that were different from the general population. In instances where genotype data from large cohorts of ethnically-diverse individuals were reported without respect to ethnicity, studies were only considered if one ethnicity was ≥95% of the majority. In some cases, sample sizes or allele frequencies were updated to reflect only subjects successfully genotyped for *HLA-B* (rather than the total sample size of the study) or to correct errata in the original publication. The combined analysis included 271 Africans, 371 non-Caucasian Americans, 14,397 East Asians, 30,640 Europeans including Caucasians worldwide, 491 Middle Easterners, 201 Oceanians, and 235 South or Central Asians (see Supplemental Tables S1 and S2; see the "Availability of Companion Documents" field).

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

High: Consistent results from well-designed, well-conducted studies.

Moderate: Sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Clinical Pharmacogenetics Implementation Consortium's (CPIC) dosing recommendations are based on weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account include *in vitro* studies of carbamazepine-stimulated T cells from patients with *human leukocyte antigen B (HLA-B)*15:02* alleles, and retrospective and prospective clinical outcome data for carbamazepine.

The evidence is graded on a scale of high, moderate, and weak, modified slightly from Valdes et al (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians. The Clinical Pharmacogenetics Implementation Consortium (CPIC) chose to use a slight modification of a transparent and simple system for just three categories for recommendations adopted from the rating scale for evidence-based recommendations on the use of retroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf) (see the "Rating Scheme for the Strength of the Recommendations" field).

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Application of a grading system to evidence linking genotypic variability to phenotypic variability indicates a high quality of evidence in the majority of cases (see Supplementary Table S3 [see the Availability of Companion Documents" field]). The evidence presented in the original guideline document and in Supplementary Table S3 provides the basis for the dosing recommendations in Table 2 in the "Major Recommendations" field.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

A potential benefit of *human leukocyte antigen B (HLA-B)*15:02* testing is a significant reduction in the incidence of serious, sometimes fatal, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) reactions to carbamazepine by identifying those who are at significant risk and recommending alternative treatments appropriate for the underlying indication. The success of *HLA-B*15:02* prospective screening in reducing the rate of SJS/TEN has recently been demonstrated clinically in a Chinese population.

Potential Harms

- A potential risk of *human leukocyte antigen B (HLA-B)*15:02* testing is ruling out the use of carbamazepine in patients who may not have developed Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN); however, this risk is mitigated by the fact that there are often alternatives to carbamazepine with comparable effectiveness.
- Another potential risk would be an error in genotyping. In the event of a false-negative result, a high-risk patient could mistakenly be prescribed carbamazepine. However, because not all carbamazepine-induced SJS/TEN can be attributed to *HLA-B*15:02*, clinicians should carefully monitor all patients as standard practice. Genotype results are associated with a patient for a lifetime, and a genotyping error could have a broader impact on health care should other *HLA-B*15:02* associations be identified in the future.
- Carbamazepine can cause a wide variety of cutaneous adverse drug reactions, including mild maculopapular eruptions (MPEs), drug hypersensitivity syndrome, in which a cutaneous eruption is associated with systemic manifestations, and SJS/TEN, the most severe manifestation.
- Above the 4–12 µg/ml therapeutic range, adverse effects include diplopia, drowsiness, nausea, and sedation. Carbamazepine adverse effects that are not clearly dose or concentration dependent include aplastic anemia, hyponatremia, leucopenia, osteoporosis, and hypersensitivity reactions such as MPEs, hypersensitivity syndrome, SJS/TEN, or drug-induced liver injury. See the original guideline document for additional details on the adverse effects of carbamazepine.
- Individuals at highest risk for the development of carbamazepine-induced SJS/TEN are those of Han Chinese descent, followed by those in Vietnam, Cambodia, the Reunion Islands, Thailand, India (specifically Hindus), Malaysia, and Hong Kong.

Qualifying Statements

Qualifying Statements

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

Recently, a systematic review by Yip et al. of the relationship between carbamazepine-induced Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and *human leukocyte antigen B (HLA-B)*15:02* showed that the positive predictive value and negative predictive value for a screening test in Asians were 1.8% (7.7% in Han Chinese only) and 100%, respectively, and that 461 patients would need to be tested to prevent one case of SJS/TEN. Furthermore, they determined that carriage of *HLA-B*15:02* in Asian patients was associated with a pooled odds ratio of 113.4 (95% confidence interval = 51.2–51.0; $P < 1 \times 10^{-5}$). Therefore, a significant percentage of the patients carrying the allele would not suffer from carbamazepine-induced SJS/TEN, and it is not currently possible to distinguish these carriers. However, the benefit of the high negative predictive value is clinically relevant, where Asian non-carriers of the risk allele are virtually at no risk to develop SJS/TEN, based on the study of Yip et al. Considering the severity of SJS/TEN, a negative test result will represent very valuable information when making treatment decisions related to carbamazepine. In the interest of patient safety, however, all patients should be monitored for cutaneous effects regardless of carrier status.

Disclaimer

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time the guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC guidelines, or for any errors or omissions.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Leckband SG, Kelsoe JR, Dunnenberger HM, George AL Jr, Tran E, Berger R, Muller DJ, Whirl-Carrillo M, Caudle KE, Pirmohamed M. Clinical Pharmacogenetics Implementation Consortium guidelines for HLA-B genotype and carbamazepine dosing. Clin Pharmacol Ther. 2013 Sep;94(3):324-8. [39 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Sep

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

Source(s) of Funding

The authors acknowledge the critical input of members of Clinical Pharmacogenetics Implementation Consortium (CPIC) of the Pharmacogenomics Research Network, particularly Mary V. Relling (St. Jude Children's Research Hospital) and Teri E. Klein (PharmGKB Stanford University), funded by the National Institutes of Health (NIH). This work is funded by NIH grants 2U19GM061390, R24 GM61374, MH92758, U19 HL065962, U01 GM092666, and U01 HL0105918.

Guideline Committee

Not stated

Composition of Group That Authored the Guideline

Authors: SG Leckband, Veterans Affairs San Diego Healthcare System, San Diego, California, Department of Psychiatry, University of California, San Diego, San Diego, California; JR Kelsoe, Veterans Affairs San Diego Healthcare System, San Diego, California, Department of Psychiatry, University of California, San Diego, San Diego, California; HM Dunnenberger, Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA; AL George, Jr., Division of Genetic Medicine, Vanderbilt University, Nashville, Tennessee; E Tran, Veterans Affairs San Diego Healthcare System, San Diego, California; R Berger, Veterans Affairs San Diego Healthcare System, San Diego, California; DJ Müller, Centre for Addiction and Mental Health, Toronto, Canada, Department of Psychiatry, University of Toronto, Canada; M Whirl-Carrillo, Department of Genetics, Stanford University, Palo Alto, California; KE Caudle, Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee; M Pirmohamed, Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom

Financial Disclosures/Conflicts of Interest

The authors declared no conflict of interest.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Pharmacogenomics Knowledgebase Web site .

Availability of Companion Documents

The following are available:

- Supplementary material, including tables and methodological information, is available from the Pharmacogenomics Knowledgebase Web site .
- An interactive dosing table is available at the Pharmacogenomics Knowledgebase Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 31, 2013. The information was verified by the guideline developer on December 6, 2013.

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